Questionable Validity of Creatinine-Based eGFR in Elderly Patients

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Article

Questionable Validity of Creatinine-Based eGFR in Elderly Patients

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Abstract: Background: Recommended CKD first-line diagnostics is based on GFR-determination by Creatinine. Cystatin C-use may provide better assessment.Methods: We compared creatinine- and cystatin C-derived eGFR determination in first-line diagnostic of 112 hospital patients aged >60 years (median=76 years). Patients were judged *kidney-sane* according to first-line diagnostic recommendations (N=61, eGFR (CKD-EPI) ≥60ml/min/m2, total urine protein <150mg/g creatinine, urinary red and white blood cells not increased) or classified *at-risk* for kidney insufficiency due to aortic valve dysfunction (N=51). Plausibility of eGFR-values was evaluated retrospectively by final case diagnoses.Results: eGFR (CAPA) was found linearly correlated to eGFR (CKD-EPI) (R2=0.5, slope=0.69, p<0.0001). In 93/112 (>80%) cases, eGFR (CAPA) yielded lower values (on average ≈20%). In 55/112 (49%) cases CKD-stage decreased. CKD-reclassification from *kidney-sane* to kidney-insufficient state (i.e., CKD1/2 to CKD3a/b or 4) or reclassification to more severe kidney insufficiency (i.e., CKD3a→3b/4 or 3b→4) was found in 41/112 (37%) cases. Worsening of CKD-classification (*kidney-sane*→kidney-insufficient) based on eGFR (CAPA) was in 30% of cases plausible in the light of final case-diagnoses.Conclusion: In elderly patients (>60 years), renal function appears systematically overestimated by creatinine-based eGFR (CKD-EPI) heralding for this group employment of cystatin C-based eGFR (CAPA) as first-line diagnostic.

Keywords: renal dysfunction; chronic kidney disease; CKD-stage; eGFR; creatinine; cystatin C

1. Introduction

Impaired kidney function and/or chronic kidney disease (CKD) is a major cause of morbidity and mortality, particularly in societies undergoing demographic change. Current worldwide prevalence of CKD is estimated at 8-16% [3]. From 1960 to 2016, death due to CKD has increased by 98% to ≈ 1.2 million per year in 2016 [4].

Detection of chronic kidney disease in first-line diagnostics is of high importance. It is a comorbidity and a severe risk factor of various diseases and influences the outcome after cardiologic interventions [5–8]. It must be taken into account for the dosage of potential nephrotoxic medications and the application of potentially kidney-damaging radiological procedures [9].

This is true for critically ill and old patients with known kidney disease or high risk for such disease. But also, for supposedly healthy patients with no known kidney disease. Two sub-aspects are relevant here: Unknown kidney damage must be detected reliably. And the stage of kidney damage must be correctly assessed.

We wanted to find out whether the guidelines for the detection of chronic kidney disease are suitable for first-line detection and classification of chronic kidney diseases in elderly patients (aged > 60 years) admitted to a hospital.

To date, non-invasive assessment of renal function and dysfunction relies mostly on laboratory tests. Clinical stages of CKD as defined by the organization for Kidney Disease: Improving Global Outcomes (KDIGO) are entirely based on GFR values [10]. The most reliable procedure for

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determining GFR is plasma clearance or urinary excretion of exogenous filtration markers such as inulin or iohexol [11,12]. However, these procedures are of little use in routine clinical health care. Measurement of the clearance of endogenous filtration markers, such as creatinine, is an alternative approach at exact GFR-determination. This approach is more practical in the clinical context. However, determination of endogenous creatinine clearance is also not widely used because it requires stringent collection of complete urine excretion over extended time periods. This procedure is cumbersome and impractical in most clinical situations. Instead, the estimation of GFR based on plasma levels of endogenous filtration markers has become the procedure of choice.

As recommended by international guidelines, initial screening of renal function is currently almost always based on GFR estimates derived from serum creatinine by the CKD-EPI formula [10]. Various formulae for calculating GFR estimates (eGFR) have been established in routine clinical diagnostics [13]. The CKD-EPI formula using serum creatinine is confounded by tubular secretion, muscle mass, food protein intake, and medication [9]. Due to these confounders, serum creatinine does not increase until GFR drops by more than 50% [14]. This limitation is crucial because a drop of GFR by more than 50% (i.e., below 60 ml/min entailing transition from CKD-stage 2 to CKD-stage 3) is associated with a significant increased mortality [15] but not detected reliably by GFR-estimates based on creatinine. This shortcoming has prompted the search for more reliable filtration markers, such as the cysteine protease inhibitor cystatin C [16]. But GFR estimates derived from serum cystatin C are rarely used and are not recommended as a primary diagnostic [10] despite several studies indicating superiority of cystatin C as marker for estimating GFR and predicting kidney function [8,16–19].

Consequently, here, we address two main questions:

1. Are kidney disease patients correctly identified by recommended first-line diagnostics?

For this purpose, we studied patients admitted to the hospital with a variety of diagnoses. These patients were selected as *kidney-sane* according to currently recommended first-line kidney diagnostics (eGFR CKD-EPI ≥ 60 ml/min and negative results of urine analysis). We rechecked their renal status by eGFR-cystatin C and used the coded diagnoses to judge the validity of the two procedures. We have here tested the CAPA formula, most widely implemented in routine healthcare.

2. Are patients with recommended first-line diagnostics assigned to the correct GFR stage?

For this purpose, we additionally studied patients considered *prima facie* at risk for chronic kidney failure due to suffering from aortic valve stenosis and therefore being lined up for TAVI. Patients undergoing transcatheter aortic valve replacement (TAVI) can be expected to have a higher incidence of CKD than the normal population [20]. In these patients we addressed the differences in the classification of manifest kidney-disfunction according to cystatin C- and creatinine-based GFR-estimations, as previously described by others [8].

The recommended strategy may be particularly unsuitable for elderly individuals, most notably for elderly hospitalized patients. These patients are afflicted by co-morbidities compromising kidney dysfunction. They are often lined up for potentially nephrotoxic iatrogenic interventions. Furthermore, they are *nota bene* subjected to age-related decline in muscle mass and residual GFR-capacity, which compromises utility of creatinin-based GFR-estimation.

2. Materials and Methods

Study Participants: A total of 112 in- and out-patients of the University Hospital of the Heinrich Heine University Düsseldorf were included and assigned to two cohorts. One cohort (N=61, 25 female, 36 male, mean age 71.89 years, median age 70.87 years) was denominated *kidney-sane* because these patients appear to be in good renal health after primary diagnostics, which are frequently used in clinical practice according to the guidelines. These patients were included based on the following criteria: age > 60 years, eGFR CKD-EPI ≥ 60 ml/min, total protein in urine < 150 mg/g creatinine or < 150 mg/l, white and red blood cell count in urine < 25/µl and < 23/µl, respectively, or corresponding negative results for white and red blood cells in urine test strip analysis. The true state of renal or non-renal diseases of these patients was determined *ex post* according to the etiology of the ICD-10-encoded diagnoses (see Appendix Table A1). We decided on this type of patient inclusion because

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for the treating physician in practice, in the primary diagnosis of patients without known CKD, it is precisely these laboratory parameters that are used to assess renal function.

The other cohort (N=51, 23 female, 28 male, mean age 81.48 years, median age of 82.69 years) was denominated *at risk (TAVI)* due to suffering from aortic valve stenosis known to increase the risk of kidney dysfunction [20]. These patients were admitted to the hospital for Transcatheter Aortic Valve Implantation (TAVI) and included in the study if aged > 60 years.

Ethics: The investigation was approved by the local ethics board of the Medical Faculty of the Heinrich Heine University Düsseldorf (study number 2022-1839). Laboratory results and ICD-10-coded diagnoses retrieved for this study were anonymized prior to data analysis. The investigation conforms to the principles outlined by the Declaration of Helsinki of the World's Medical Association. All patients have given informed consent.

Laboratory analyses

All analyses were performed by accredited standardized diagnostic procedures as part of routine diagnostic workup of the participants. Li-heparine-plasma or serum was obtained by vein puncture. Samples were analyzed within 2 h or stored for reflex testing at -20 °C for not more than eight weeks. Creatinine and cystatin C were determined on a Cobas 8000 analyzer (Roche; Basel, Switzerland) by enzymatic assay and particle-enhanced immunological turbidity assay, respectively.

Traceability: The method of creatinine determination was standardized against ID/MS (isotope dilution mass spectrometry) according to the manufacturer's instructions. The method of cystatin determination was standardized against the ERM-DA471/IFCC reference material according to the manufacturer's instructions.

Calculation of eGFR

Creatinine-based GFR estimates were calculated according to the CKD-EPI formula [1], as follows: Females, plasma creatinine ≤ 0.7 mg/dl:

$GFR_{CKD\text{-}EPI} = 144 \times (\text{Creatinine [mg/dl]} / 0.7)^{-0.329} \times 0.993^{age}$;

females, plasma creatinine > 0.7 mg/dl:

$GFR_{CKD\text{-}EPI} = 144 \times (\text{Creatinine [mg/dl]} / 0.7)^{-1.209} \times 0.993^{age}$;

males, plasma creatinine ≤ 0.9 mg/dl:

$GFR_{CKD\text{-}EPI} = 141 \times (\text{Creatinine [mg/dl]} / 0.9)^{-0.411} \times 0.993^{age}$;

males, plasma creatinine > 0.9 mg/dl:

$GFR_{CKD\text{-}EPI} = 141 \times (\text{Creatinine [mg/dl]} / 0.9)^{-1.209} \times 0.993^{age}$.

Cystatin C–based GFR estimates were calculated according to the CAPA formula [2]:

$GFR_{CAPA} = 130 \times \text{Cystatin C [mg/l]}^{-1.069} \times age^{-0.117} - 7$.

Statistics

Graph Pad Prism 9 (Graph Pad Software, Inc., San Diego, CA, USA: released in 2020. Graph Pad Prism 9 for Mac, San Diego, CA, USA: Graph Pad Inc.) and Microsoft Excel (Microsoft, Redmond, WA, USA: released in 2022. Microsoft Excel for Mac Version 16.67 Redmond, WA, USA: Microsoft Corp.) were used for analysis. Data were descriptively analyzed by mean and median values. Normal distribution was tested according to Shapiro-Wilk. Correlations were analyzed by Spearman's correlation and assumed to be good at $r \geq 0.7$ and moderate at $r \geq 0.5$. Differences were analyzed by the Wilcoxon test for paired samples. For all tests, statistical significance was assumed at $p < 0.05$.

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3. Results

3.1. Cystatin C-based eGFR (CAPA) is linearly correlated with, but almost always lower than, creatinine-based eGFR (CKD-EPI)

Across the entire population of 112 elderly patients a systematic downward bias of cystatin C-based eGFR relative to creatinine-derived eGFR (CKD-EPI) was indicated by linear regression of the two datasets, yielding

eGFR(CAPA)=0.6880*eGFR(CKD-EPI)+9.246,

(R^2 = 0.498, p < 0.0001) (Figure 1). Of note, at eGFR > 40 ml/min regression line and 95% confidence interval of regression were far beneath the hypothetical line of identity, supporting the notion that moderate decreases in GFR are indicated by cystatin C-based eGFR but not by creatinine-based eGFR.

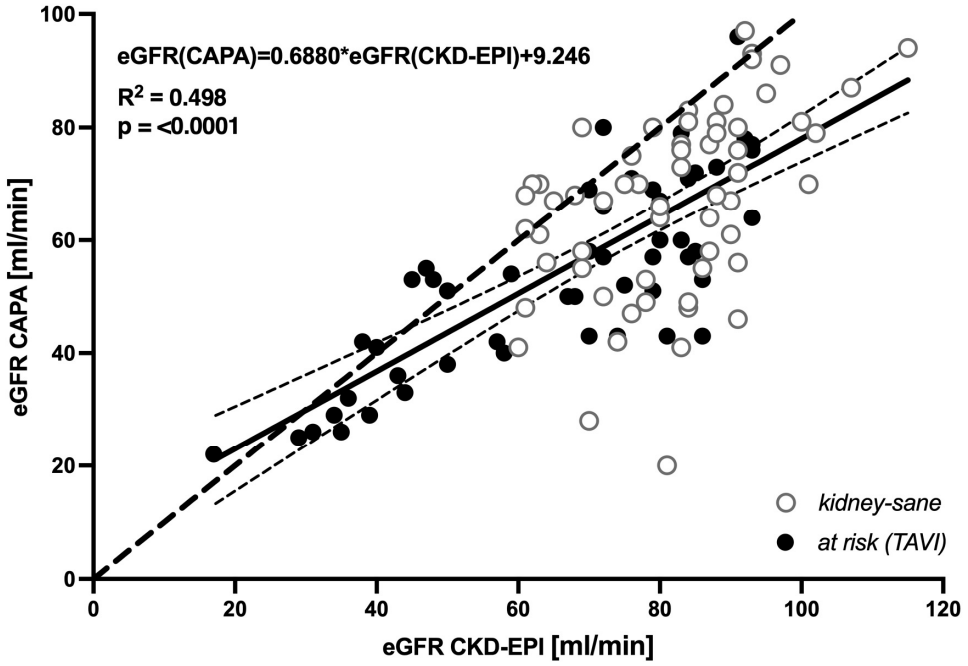

Figure 1. Linear Regression of eGFR CKD-EPI and eGFR CAPA: Cumulated results obtained for *kidney-sane* (N=61, open circles) and *at risk (TAVI)* cases (N=51, closed circles). Each data point represents one patient. Solid line: linear regression of the values. Thin dotted lines: 95%-confidence intervals of linear regression. Thick dotted line: Hypothetical identity of results.

Correspondingly, in a vast majority of the analyzed cases, cystatin C-based eGFR was distinctively lower than creatinine-based eGFR. This was likewise true for the *kidney-sane* patients (Figure 2 left panel) and for the *at risk (TAVI)* patients suffering from manifest kidney disease or bearing an increased risk therefore (Figure 1 right panel). Cystatin C-derived eGFR was lower than creatinine-derived eGFR in ≈ 84% of *kidney-sane* and ≈ 82% of *at risk (TAVI)* cases.

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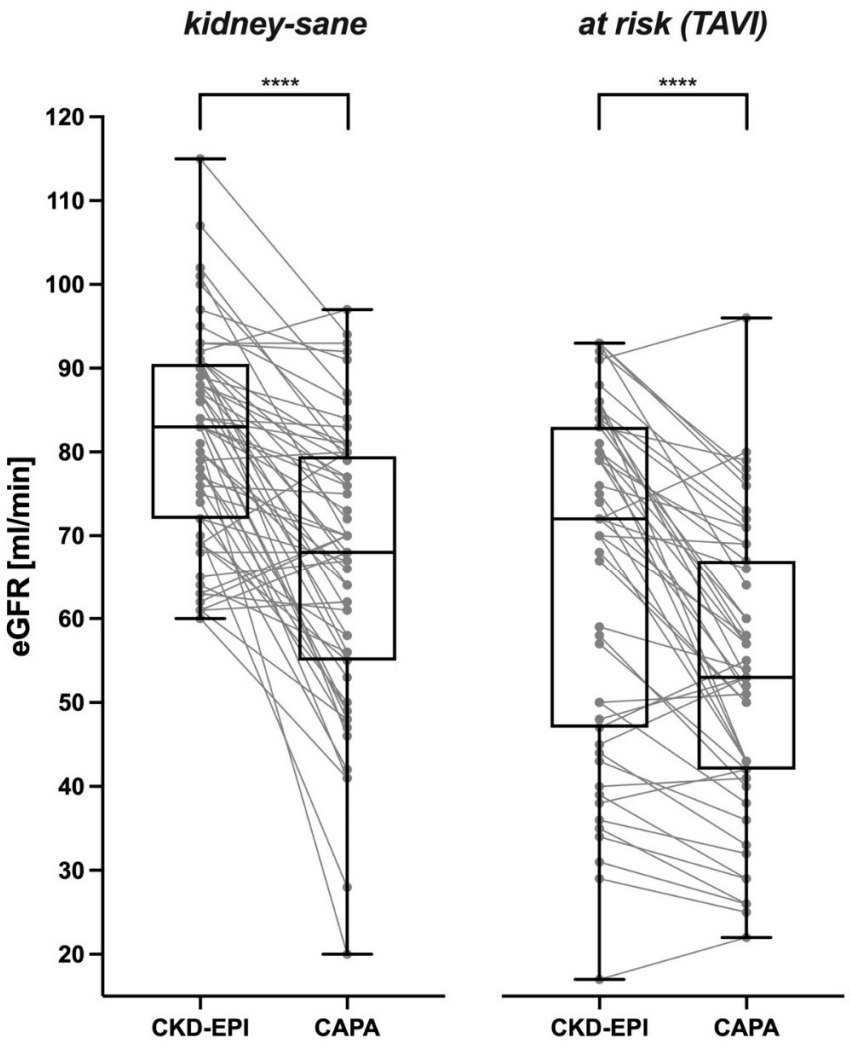

Figure 2. Individual differences between eGFR CKD-EPI and eGFR CAPA: Results obtained for the *kidney-sane* group (left) and the *at risk (TAVI)* group (right). Each data point represents one patient. Corresponding eGFR results obtained by CKD-EPI and CAPA are joined by lines. Box plots show quartiles. Horizonal line represents the median. Vertical line represents upper and lower whisker with range of values.

In the *kidney-sane* patients CKD-EPI-calculated eGFR was 81.56 ± 12.41 ml/min in the mean and 83 ml/min in the median. In contrast, eGFR derived from serum/plasma cystatin C (CAPA formula) was 66.38 ± 16.60 ml/min in the mean and 68 ml/min in the median. The prevalent downward bias of cystatin C-based eGFR (-21.35 ± 18.64 and -13.50 ± 18.31% for males and females, respectively) was highly significant ($p < 0.0001$).

The *at risk (TAVI)* patients exhibited lower eGFR values than the *kidney-sane* patients. CKD-EPI-derived eGFR was 66.14 ± 20.71 ml/min in the mean and 72 ml/min in the median. Nevertheless, cystatin C-based eGFR was even lower (53.53 ± 16.92 ml/min in the mean and 53 ml/min in the median). Again, the downward bias of cystatin C-based eGFR (-15.70 ± 19.16 and -18.09 ± 14.53% for males and females, resp.) was highly significant ($p < 0.0001$).

3.2. Potential impact of eGFR (CAPA) on CKD-stage and clinical classification of kidney disease

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Since in both groups cystatin C-based eGFR (CAPA) was notably lower than eGFR (CKD-EPI), the question arose whether the use of eGFR (CAPA) instead of eGFR (CKD-EPI) would result in assignments of the patients to different CDK-stages. This question seemed particularly interesting for the *kidney-sane* group, i. e. the patients classified as not suffering from kidney disease according to eGFR (CKD-EPI). While half of these patients (50.82%) remained in the same CKD-stage upon reclassification according to eGFR (CAPA), the rest moved one (36.07%), two (9.84%) or even three (3.28%) CKD-stages downwards (Figure 3, left). More relevant, for one third of these patients, reclassification according to eGFR (CAPA) resulted in a CKD-stage indicative of kidney dysfunction or even kidney disease, while all these patients were judged *kidney-sane* according to eGFR (CKD-EPI). Thus, reclassification did not only alter CKD-stage but also clinical classification of kidney disease state for a significant portion of the patients. A similar observation was made in the *at risk (TAVI)* group: Half of these (49.02%) were down-graded by one or two CKD-stages (Figure 3, right), and 27.45% of the cases were moved to a worse clinical disease classification, i. e. from CKD-stages 1/2 to CKD-stages 3a/b or even 4 (Figure 4). It should be noted that there was not a single patient in both groups, whose CKD-stage or disease classification improved when based on eGFR (CAPA) instead of eGFR (CKD-EPI).

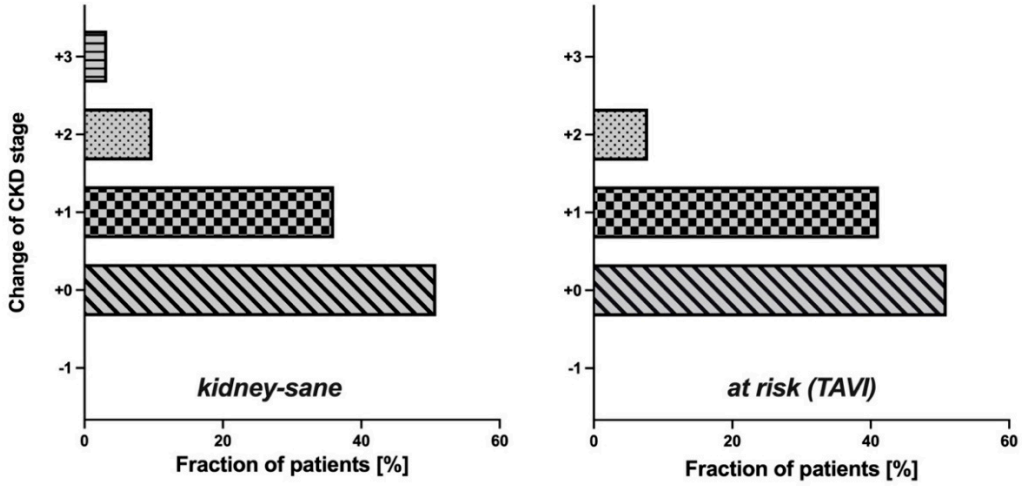

Figure 3. CKD restaging based on eGFR CAPA: Bars show percentage of patients. Left: *kidney-sane*. Right: *at risk (TAVI)*.

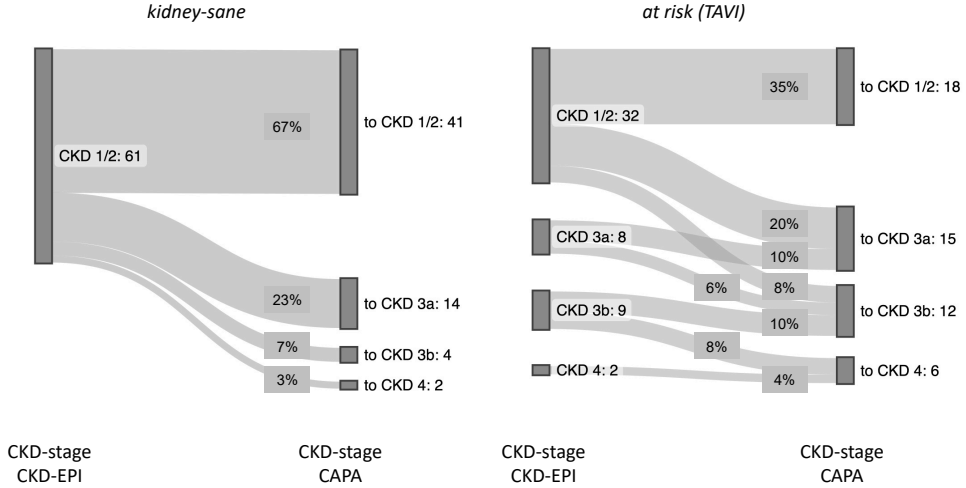

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Figure 4. CKD-restaging based on eGFR CAPA: Flows show proportions of patients per stage. Restaging from CKD-EPI (left) to CAPA (right). Left diagram: *kidney-sane*. Right diagram: *at risk (TAVI).*

Overall, the *kidney-sane* patient collective was entirely assigned to CKD-stage 1 or 2 according to eGFR (CKD-EPI) and gained roughly one third of cases of more or less advanced kidney insufficiency, when reclassified according eGFR (CAPA). Similarly, in the *at risk (TAVI)* group roughly one more third of the cases was judged to be at risk for chronic kidney failure, when analyzed according eGFR (CAPA) (summarized in Figure 5).

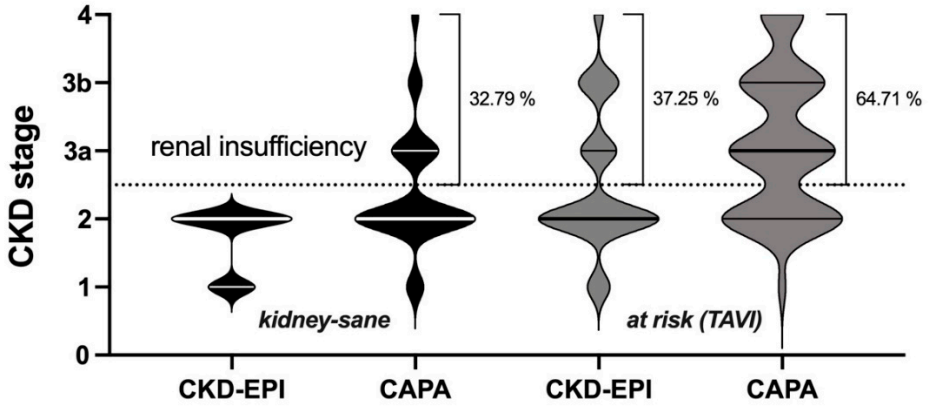

Figure 5. Distribution of CKD stages based on eGFR CKD-EPI and eGFR CAPA: CKD stages obtained for *kidney-sane* (left) and TAVI-patients (right). Violins: proportion of patients. Thick lines: medians, thin lines: quartiles. Dotted line: border between renal sufficiency and insufficiency. Brackets: proportion of patients classified as renal insufficient.

3.3. Sensitivity of eGFR (CKD-EPI) and eGFR (CAPA) for kidney-relevant clinical diagnoses

To test whether the reclassification according to eGFR (CAPA) from presumably *kidney sane* to presumed renal insufficiency (i.e., from CKD ≤ 2 to CKD > 2) was plausible in clinical terms, we unblinded the ICD-10-coded diagnoses of the (based on laboratory parameters) *kidney-sane* group and therefrom identified etiologies plausibly encompassing or entailing kidney dysfunction or not. As summarized in Table 1, the vast majority (> 90%) of those patients remaining in CKD-stage 1 or 2 after recalculation of eGFR using cystatin C were indeed not diagnosed to suffer from primary or secondary renal disease. In contrast, a significant fraction (30%) of those patients that according to eGFR (CAPA) were moved from *kidney-sane* to kidney insufficient state (i.e., from CKD stage ≤ 2 to CKD-stage >2) had indeed diagnoses encompassing renal insufficiency.

Table 1. Diagnoses related to CKD-reclassification of *kidney-sane* group.

Reclassification (eGFR - CAPA)	N (%)	Etiologies[1]
Remained CKD-stage 1/2	3 (7)	**Renal disease:**
		Acute or chronic kidney disease (1)
		Neoplasia (kidney) or loss of kidney (2)
	38 (93)	**Non-renal disease:**
		Arthropathy (1)
		Autoimmune disease (2)
		Cardiovascular disease (1)
		Disease of the bile ducts (1)
		Disease of the eyes (2)
		Hematological disease (2)

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		Infectious disease (1) Neoplasia/dysplasia (non-renal) (7) Neurological disease (4) Rheumatic disease (13) Unknown/others (4)
Reclassified CKD-stage 3a, 3b or 4	6 (30)	**Renal disease:** Acute or chronic kidney disease (3) Kidney transplant (1) Neoplasia (kidney) or loss of kidney (2)
	14 (70)	**Non-renal disease:** Autoimmune disease (2) Disease of the eyes (1) Dysphagia (1) Flanks/abdominal pain (2) Gait and mobility disorders (1) Infectious disease (1) Neoplasia/dysplasia (non-renal) (3) Rheumatic disease (3)

[1] Derived from ICD-10-encoded diagnoses (Suppl. Tab 1).

4. Discussion

4.1. Sensitivity of first-line diagnostic for kidney dysfunction

Our data suggest that in multimorbid elderly persons (as typically hospitalized in a university hospital) GFR-estimations based on serum creatinine according to the CKD-EPI formula are prompting an over-optimistic clinical assessment of kidney function. As a consequence, unknown/hidden kidney disease is overlooked in up to 30% of cases with undetermined state of kidney function. In the collective of elderly hospitalized patients analyzed here GFR-estimation based on cystatin C appeared more sensitive for, and less prone to overlooking, manifest kidney insufficiency than creatinine-based GFR estimations. Our observation that GFR is frequently underestimated by the CKD-EPI formula in elderly patients is plausible, given that the CKD-EPI formula has been developed based on a collective encompassing relatively few individuals aged 60 years or more [1]. Moreover, the here observed downward bias of serum cystatin C-based relative to creatinine-based GFR-estimates conforms to many previous findings [8,16,21].

4.2. Correct assessment of CKD-stage

Our data obtained in a group of TAVI patients suggest that severity of manifest kidney disease is often underestimated by GFR-estimates based on serum creatinine according to the CKD-EPI formula. In the case of TAVI patients under-determination of kidney insufficiency is particularly unfortunate, because patients with renal dysfunction have a worse outcome after TAVI [6–8]. In addition to the current status assessment of renal function, the GFR determined by cystatin C in TAVI patients with a GFR of 3b or worse also seems to be better suited for the prognostic assessment of the patients. This is true for the risk of cardiovascular and cerebrovascular impairment [8].

This is relevant, because our data show that the proportion of these patients is in fact higher than assumed according to standard diagnostics. Thus, correct pre-interventional assessment of renal function is essential for post-interventional monitoring of these patients.

4.3. What is the ultimative filtration marker?

In agreement with many previous studies [8,16–19], our data strongly suggest that cystatin C is superior to creatinine as a filtration marker. Nevertheless, cystatin C based eGFR estimates can also be subject to error, because serum levels of cystatin C are confounded by extra-renal factors such as

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age, gender, body mass, body length, cigarette smoking, high low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol, obesity, diabetes and inflammation [22,23]. Moreover, the clinical relevance of differences between eGFR values based on cystatin C and creatinen seems unclear. Thus, it has been shown that the use of eGFR-CKD-EPI-Cystatin C (in contrast to the CAPA-formula employed here), especially to predict disease progression and mortality in patients with mild CKD, offers no benefits and only increases costs [24].

Given the limitations of both creatinine and cystatin C, other markers for measuring kidney function are currently the subject of research. In critically ill sepsis patients, for example, proenkephalin exhibited a more precise correlation with the GFR than creatinine [25,26]. Unfortunately, proenkephalin has not yet been extensively compared to cystatin C. Thus, it remains to be found out whether it is superior to it.

4.4. Limitations of our study

Limitations of our study are the small case number and the lack of GFR-validation by a gold-standard GFR procedure. However, since many studies show that cystatin C appears superior to creatinine, it seemed sufficient to evaluate the additional value of cystatin C as compared to creatinine in terms of clinical utility.

5. Conclusions

In the first-line diagnostics of elderly, hospitalized patients for the detection of previously unrecognized renal dysfunction, the sole use of creatinine as a GFR marker seems insufficient. Nevertheless, this procedure is still recommended in the German S2k Interdisciplinary Guidelines and the international KDIGO Guidelines [10,27].

Furthermore, creatinine-based GFR estimation underestimates existing renal dysfunction compared to cystatin C-based measurement..

Pending corroboration by a larger study, our result suggest that a modification of guidelines and recommendations with respect to elderly hospitalized patients could be heralded. It could be imagined that elderly hospitalized patients would significantly profit from cystatin C derived determination of eGFR (CAPA) as obligatory diagnostic reflex, whenever creatinine-based eGFR (CKD-EPI) appears normal (i.e., is above 60 ml/min).

Author Contributions: Conceptualization, D.G. and F.B.; methodology, D.G. and F.B.; software, Graph Pad Prism 9 (Graph Pad Software, Inc., San Diego, CA, USA: released in 2020. Graph Pad Prism 9 for Mac, San Diego, CA, USA: Graph Pad Inc.) and Microsoft Excel (Microsoft, Redmond, WA, USA: released in 2022. Microsoft Excel for Mac Version 16.67 Redmond, WA, USA: Microsoft Corp.); data curation, D.G., R.E.W., L.H.; writing—original draft preparation, D.G. and F.B.; writing—review and editing, D.G. and F.B..; visualization, D.G. and F.B.; helpful discussions: R.E.W, L.H.. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (study number 2022-1839, 07.02.2022).” for studies involving humans

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflict of interest.

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Abbreviations

CAPA	Caucasian, Asian, Pediatric and Adult
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CVD	cardiovascular disease
eGFR	estimated Glomerular Filtration Rate
GFR	Glomerular Filtration Rate
ICD-10	International Statistical Classification of Diseases and Related Health Problems
IFFC	International Federation of Clinical Chemistry and Laboratory Medicine
KDIGO	Kidney Disease: Improving Global Outcomes
TAVI	Transcatheter Aortic Valve Implantation

Appendix

Table A1. caption.

etiology	Main or kidney-relevant secondary diagnosis (ICD-10-encoded)
Renal disease	
Acute or chronic kidney disease	*Chronic* kidney disease *Acute* renal failure, Crush kidney with acute renal failure *State* after acute renal failure
Kidney transplant	*Follow-up* examination after organ transplantation *condition* after kidney transplantation
Neoplasia (kidney) or loss of the kidney	*Multilocular* cystic neoplasia of the kidney with low malignancy potential, status after renal cell carcinoma *Loss* of kidneys, Follow-up care after living kidney donation *Pulmonary* and osseous metastatic renal cell carcinoma *Malignant* neoplasm of the kidney, angiomyolipoma at the upper pole of the right kidney
Non-renal disease	
Athropathy	*Other* unspecified crystal athropathies: shoulder region
Autoimmune disease	*Progressive* systemic sclerosis, other overlap syndromes, seronegative chronic polyarthritis: multiple localizations *Other* giant cell arteritis *MS* with a secondary chronic course with indication of an acute exacerbation or progression *Other* forms of systemic lupus erythematosus
Cardiovascular disease	*Arterial* hypertension WHO grade II, no sec. cause of hypertension
Disease of the bile ducts	*Cholecystolithiasis*
Disease of the eyes	*Suspected* scleritis *Zoster* ophthalmicus *Corneal* dystrophy
Dysphagia	*Other* and unspecified dysphagia
Flanks/abdominal pain	*Pain* localized in other parts of the lower abdomen *Other* and unspecified abdominal pain, Personal history of malignant neoplasms of other organs or systems, Hypothyroidism after medical interventions
Gait and mobility disorders	*Weakness*
Hematological disease	*Anemia* *Status* after hematopetic stem cell transplantation, acute myeloid leukemia
Infectious disease	*Vesicular* stomatitis with enterovirus exanthema *Infection* by corona viruses of unspecified location

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Neoplasia/dysplasia (non-renal)	*Malignant* neoplasm of the rectum
	Prostate dysplasia, Foreskin hypertrophy, phimosis and paraphimosis
	Prostate adenocarcinoma
	Malignant neoplasm of the prostate
	Malignant neoplasm in the temporal lobe
	Malignant neoplasm in the frontal lobe
	Olfactory meningioma
	Malignant neoplasm: urinary bladder, several parts overlapping
	Hepatocellular carcinoma
	Locoregionally recurrent, bipulmonary and lymphogenous metastatic p16-positive oropharyngeal carcinoma
Neurological diseases	*Uninhibited* neurogenic voiding, not elsewhere classified
	Cerebral infarction due to embolism of cerebral arteries
	Gait disturbance/ataxia
Rheumatic disease	*Other* seropositive chronic polyarthritis: Multiple localizations
	Other seropositive chronic polyarthritis: Multiple localizations, systemic lupus erythematosus involving organs and organ systems
	Other specified chronic polyarthritis: several localizations
	Seronegative chronic polyarthritis: multiple localizations
	Felty syndrome: Multiple localizations
	Psoriatic arthropathy
	Polymyalgia rheumatica
	Giant cell arteritis in polymyalgia rheumatica, other polyarthrosis
	Wegener's granulomatosis
Unknown/others	*Unknown*
	Follow-up control with no evidence of neoplasia
	Preliminary examination: living kidney donation

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